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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,131	GOLDSPINK, GEOFFREY	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-96* is/are pending in the application.

4a) Of the above claim(s) *36-40,43-48,52-57,63-66,70-75 and 79-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-35,40-42,49-51,58-62,67-69 and 76-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application was filed December 5, 2001. It is a continuation of 09/403,707 filed October 22, 1999, now abandoned. 09/403,707 is the National stage of PCT/GB98/01198 filed April 25, 1998. Applicant claims foreign priority to application 9708526.0 filed in the United Kingdom, April 25, 1997.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on April 25, 1997. It is noted, however, that applicant has not filed a certified copy of the 9708526.0 application as required by 35 U.S.C. 119(b).

Election/Restrictions

Applicant's election with traverse of Group III in the reply filed on August 18, 2004 is acknowledged. The traversal is on the ground(s) that Groups I through VI do not represent the entire scope of the pending claims 31-96. The Applicant asserts that none of the Groups are drawn to methods of administering a plasmid vector comprising a light chain enhancer and a viral promoter operatively linked to a sequence that generates a polypeptide; further none of the Groups are drawn to methods of administering a viral vector comprising a myosin light chain enhancer and viral promoter operatively linked to a sequence that generates a polypeptide. The traversal is additionally based on the grounds that claims 67 and 69 were not included in any of the Groups I through VI. The Applicant also asserts that the there is not a serious search burden on the Examiner as the subject matter of the claims of Groups I through VI are

intertwined that a search would identify any relevant art pertaining to a plasmid or viral vector containing a myosin light chain enhancer.

Concerning the issue that Groups I through VI do not represent the entire scope of the pending claims, this argument is not found persuasive because the other embodiments of vector constructs are encompassed by claim 31. Claim 31 is a linking claim. This means that Groups I through VI and all other embodiments defined by claim 31 are encompassed by claim 31. Groups I through VI were established because they appeared to be six specific embodiments. Concerning the issue that claims 67 and 69 were not included in any of the Groups, the Examiner corrects the error by including claims 67 and 69 in Groups I through IV. With regards to the argument that there is not a serious search burden on the Examiner in finding relevant art, the Examiner disagrees. Each of Group I through VI is a unique construct and each functions differently. Furthermore, Groups V and VI therapeutic agent, a polypeptide, is materially and functionally different from therapeutic RNA in Groups I through IV.

The requirement is still deemed proper and is therefore made FINAL.

Upon review of Group III, it is noted that claims 36-39 and 63-66 have been incorrectly included in the group. Group III is to a viral promoter and claims 36-39 and 63-66 are to a myosin heavy chain promoter, which is not a viral promoter. Thus, claims 36-39 and 63-66 have been excluded from Group III. The claims to be examined for Group III are: 32-35, 40-42, 49-51, 58-62, 67-69, 76-78. Claim 31 is a linking claim.

Claims 36-40, 43-48, 52-57, 63-66, 70-75, 79-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 32-35, 40-42, 49-51, 58-62, 67-69, 76-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plasmid vector comprising a myosin light chain enhancer and a viral promoter operatively linked to a polynucleotide sequence encoding a polypeptide, does not reasonably provide enablement for a plasmid vector comprising a myosin light chain enhancer and a viral promoter operatively linked to a sequence that generates a therapeutic RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

With regards to the use of "therapeutic RNA," it should be pointed out that this terminology refers to RNA molecules such as RNAi, ribozymes, and antisense. Claims 50 and 77 specifically point to antisense. "Therapeutic RNA," for purposes of this examination does not encompass mRNA which can be translated into polypeptides and proteins. The major issue that claims 32-35, 40-42, 49-51, 58-62, 67-69, 76-78 raises

concerning "therapeutic RNA," is that the use of RNA molecules such as RNAi, ribozymes, and antisense RNA to predictably and routinely effect a biological change is not known in the art. Rather there have been many examples where the introduction of RNA molecules for purposes of gene therapy have resulted in unexpected results. By way of example, and in no way limiting, a review by Agrawal and Kanimalla (2000, Molecular Medicine Today, 61: 72-81) teaches that the use of antisense as a means of targeting a gene is unpredictable. "A good part of nucleotide design for its target RNA varies significantly, depending on base composition and sequence. Therefore, the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence. Introduction of oligonuclotides that contain certain sequence motifs, such as CpG and GGGG (hyper-structure-forming sequences) induce cell proliferation and immune responses.... If an antisense oligonuclotide possess self-complementarity or a palindromic sequence, it can form stable secondary structures such as short linear duplexes or hairpins. In such cases, secondary structure formation competes for binding to the target mRNA. In addition, these secondary structures can serve as decoys by binding to cellular factors, thereby inhibiting or inducing the functions of non-targeted genes, which could directly or indirectly alter the function of the gene being studied (page 77, second column, "Choice of oligonucleotide sequences," first and second paragraphs)." Thus, because not all antisense constructs will function as predicted, all antisense constructs need to be tested for function and efficacy. The specification does not provide any examples of antisense constructs that were able to reduce the expression level of a target gene and thus does not enable one

skilled in the art to make and/or use a plasmid vector expressing therapeutic RNA in the treatment of an animal.

Claims 31, 32-35, 40-42, 49-51, 58-62, 67-69, 76-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification states on page 5 that a "polynucleotide sequence of interest is intended to cover nucleic acid sequences which are capable of being at least transcribed. The sequences may be in the sense or antisense orientation with respect

to the promoter. Antisense constructs can be used to inhibit the expression of a gene in a cell according to well-known techniques," the art shows that the method of expressing antisense RNA to block expression of a gene is not reliable and thus not predictable. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the Applicant stated that antisense constructs can be used, however, fails to describe representative number of species encompassed by the claims. As discussed earlier in the Enablement section, not all antisense RNA molecules reliably inhibit target genes. The specification has not taught any antisense RNA molecules that inhibit target genes in the specification. Further, the specification has not described predictable ways to generate any antisense RNA encompassed by the claims. Characterization is not adequate if one supplies a nucleotide sequence or a protein sequence. To determine if an antisense RNA can block the eventual expression of a target protein entails testing that RNA's ability to block protein expression. The skilled artisan cannot envision from a sequence whether an antisense RNA will block protein expression, and therefore conception is not achieved until reduction to practice has occurred, regardless of the

complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no antisense RNA meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants attention is drawn to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein it was stated:
In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its

definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers,* 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Because Applicants have failed to provide an adequate written description of the materials used in the compositions and methods claimed and because there is no evidence that Applicants possessed any antisense RNA beyond that disclosed and/or known in the prior art, the rejected claims fail to meet the written description requirement under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 31, 32-35, 40-42, 51, 58-62, 67-69, 78 are rejected under 35 U.S.C. 102(a) as being anticipated by Novo et al. (1997, Gene Therapy, 4: 488-492). Novo et al. teach that a vector that was used to express α-galactosidase (α-gal) was comprised of a CMV promoter and of a myosin light chain enhancer. One particular vector, pX7F, was used in a series of expression experiments. When fibroblasts from a hemizygous Fabry patient (which shows low α-gal activity) are cultured with media conditioned by C2C12 myoblasts transfected with pX7F, the fibroblasts have significantly higher levels of α-gal as compared to fibroblasts that were cultured in media conditioned by C2C12 myoblasts that were not transfected with pX7F. Further, when fibroblasts were cultured with media conditioned by C2C12 myoblasts transfected with pX7F and in the presence of mannose-6-phosphate, the level of α-gal activtity in fibroblasts is completely abolished. These in vitro results suggest that the increase in the fibroblasts' activity of α-gal was the result of uptake of the enzyme via mannose-6-phosphate receptors. Further, the fact that α-gal activity was measurable indicated that the post-translational modifications of α-gal were occurring correctly (page 489, second column, second paragraph, line 13 to page 491, first column, first paragraph). Novo et

al. also teach that mice injected with pX7F in their muscle could express α-gal (page 491, first column, second paragraph, lines 1-23; see also Figure 4).

Claim 31 is rejected under 35 U.S.C. 102(a) as being anticipated by Oshima, et al. (1997, PNAS, 94: 2540-2544, see IDS). Ohshima et al. teach that the α-gal A deficient mice are a model of Fabry disease. In their study, Ohshima et al. teach how to make the α-gal A deficient mouse and described the phenotypic analysis of the mouse. One way to demonstrate that only the α-gal A gene was disrupted in these mice, was to show that α-gal A fibroblasts from the mice could be rescued by expression of α-gal A (page 2542, second column, second paragraph to page 2543, first column, first paragraph). α-gal A deficient fibroblasts transduced with a retroviral construct expressing human α-gal A were corrected of their deficiency of enzymatic activity.

Ohshima et al.'s study, while not encompassed by the specific elements of Group IV (a method of treating comprising a viral vector and a viral promoter) does read on some of its broader claims and thus anticipates these broader claims and claim 31, the linking claim. Citing Ohshima et al.'s study does not imply that Groups III and IV be rejoined. Rather, it emphasizes the point that the Restriction was proper, as Ohshima et al.'s study would not have appeared on a search for Group III (plasmid vector and viral promoter). Ohshima et al.'s study was made mention because it was provided as an IDS.

Claims 31-34, 40, 41,51, 59-61, 67, 68, 78 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiner et al. (Patent No. 5,830,876, issued November 3, 1998). Weiner et al. teach a method of immunizing an individual against a pathogen. Weiner et al. teach that a genetic construct of genetic vaccines comprise a nucleotide sequence that encodes a target protein operably linked to regulatory elements needed for gene expression (column 9, lines 39-41). When taken up by a cell, the genetic construct which includes the nucleotide sequence encoding the target protein operably linked to the regulatory elements may remain present in the cell as a function episomal molecule or it may integrate into the cell's chromosomal DNA. DNA may be introduced into cells where it remains as separate genetic material in the form of a plasmid (column 9, lines 46-52). Weiner et al. teach that the necessary elements of a genetic construct of a genetic vaccine include a nucleotide sequence that encodes a target protein and the regulatory elements necessary for expression of that sequence in the cells of the vaccinated individual. The regulatory elements are operably linked to the DNA sequence that encodes the target protein to enable expression. The nucleotide sequence that encodes that target protein may be cDNA, genomic DNA, synthesized DNA (column 9, line 64 to column 10, line 4). Weiner et al. teach examples of promoters useful for RNA expression, including, but not limiting to cytomegalovirus promoter (column 10, lines 25-32). Weiner et al. teach that in addition to regulatory elements required for DNA expression, other elements may also be included in the DNA molecule. Such additional elements include enhancers (column 10, lines 38-40).

Weiner et al. also teach that their construct, pM160 was injected into mice intramuscularly (column 24, lines 14-15).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35, 40, 62, 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner et al. (Patent No. 5,830,876, issued November 3, 1998), in view of Donoghue et al. (1998, Genes Dev. 2: 1779-1790; see NCBI printout) and Steffy and Weir (1991, J. Virol. 65: 6465-6460).

Weiner et al. teach that the necessary elements of a genetic construct of a genetic vaccine include a nucleotide sequence that encodes a target protein and the regulatory elements necessary for expression of that sequence in the cells of the vaccinated individual. The regulatory elements are operably linked to the DNA sequence that encodes the target protein to enable expression. The nucleotide sequence that encodes that target protein may be cDNA, genomic DNA, synthesized DNA (column 9, line 64 to column 10, line 4). Weiner et al. also teach examples of promoters useful for RNA expression, including, but not limiting to cytomegalovirus promoter (column 10, lines 25-32). Weiner et al. teach that in addition to regulatory elements required for DNA expression, other elements may also be included in the DNA

molecule. Such additional elements include enhancers (column 10, lines 38-40). While Weiner et al. generally teach elements that are needed for gene expression in a plasmid, they do not teach the use of specific elements such as the myosin light chain enhancer and the herpes simplex virus promoter.

Donoghue et al. teach the sequence of a muscle-specific enhancer isolated from rat (Genbank No. X14726).

Steffy and Weir teach the mutational analysis of two herpes simplex virus type 1 late promoters. In addition to demonstrating the activity of the non-mutant promoters vgCL5 (first sequence shown in Figure 2) and vgHL1 (first sequence shown in Figure 4), Steffy and Weir show that mutating certain regions of these promoters can increase or decrease gene transcription activity.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to take the general teachings of Weiner et al. and synthesize a plasmid that included the sequence of myosin light chain enhancer, provided by Donoghue et al., with the intent of expressing the plasmid in muscle. It would have also have been obvious to take the general teachings of Weiner et al. and use a herpes simplex virus type 1 late promoter, given the teachings of Steffy and Weir.

One having ordinary skill in the art would have been motivated to create a vector with a muscle specific enhancer and with a different viral promoter as work by Donoghue et al. and Steffy and Weir show that these regulatory elements can be used to drive gene expression.

There would have been a reasonable expectation of success given the results of Donoghue et al. and Steffy and Weir demonstrating that the enhancer expresses in muscle and that vgCL5 and vgHL1 are viable herpes simples virus promoters.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

The post-filing art made of record and not relied upon is considered pertinent to applicant's disclosure. Weiner et al. in Patent No. 6,733,994 B2, issued May 11, 2004 can be read onto some claims presented by the Applicant.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is (571) 272-2911. The examiner can normally be reached on Monday-Friday 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, Ph.D. can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JH

/Joe Woitach/
AU1637